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Bioavailability of oral micronized progesterone*

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Progesterone (P) has not been administered orally because of reportedly poor bioavailability and a rapid clearance rate. Unfortunately, the synthetic derivatives, although orally active, have a number of disadvantages and fail to mimic natural P completely. To investigate the bioavailability and short-term toxicity of oral micronized P, a standardized dose of 200 mg of micronized P was administered to nine healthy postmenopausal women and one male subject. Serial determinations of serum P concentrations demonstrated rapid absorption of P. Peak concentrations of P rose from a negligible baseline level to 17.0 ± 4.9 ng/ml at an average of 2.8 ± 0.35 hours after administration. The peak concentrations of P were equivalent to those observed in the midluteal phase in normal control cycles (14.1 ± 2.7 ng/ml). All subjects exhibited significant elevation of P over baseline levels that persisted for at least 6 hours after the single oral dose and returned to initial levels by 24 hours. There was no significant change in estradiol, follicle-stimulating hormone, luteinizing hormone, cortisol, aldosterone, lipids, or hepatic enzymes during the 24-hour study interval. Fertil Steril 44:622, 1985

Progestins are administered for a wide variety of clinical indications, which include oral contraception, adjunctive therapy in menopause, endometrial hyperplasia or carcinoma, endometriosis, dysfunctional uterine bleeding, amenorrhea, luteal phase inadequacy, and the premenstrual syndromes.[1] Unfortunately, the oral route of administration of naturally occurring progesterone (P) has not been practical because of the rapid hepatic metabolism and the poor bioavailability of this steroid.[2] Thus, synthetic derivatives (e.g., norethindrone acetate, norgestrel, medroxyprogesterone acetate, lynestrenol, ethynodiol diacetate, and norethynodrel) have been the only orally active progestational agents available. The synthetic progestins suffer from a number of disadvantages. None of these agents have effects identical to natural P. Certain derivatives exhibit prominent side effects, which include masculinization of the patient or fetus, depression, fluid retention, headaches, alterations in serum lipid profiles, and possible teratogenicity.[1-3] In addition, these synthetic progestins demonstrate variable antiestrogenic, estrogenic, and antiovulatory activity.[1-3]

Because of these problems, investigation has been rekindled in the search for an orally active form of natural P. Recent preliminary studies[1, 4-7] suggest that a micronized form of natural P is readily absorbed orally and may offer a novel alternative to the synthetic agents.

This study was designed for evaluation of the bioavailability and short-term toxicity of oral micronized P in an easily prepared dosage.

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Table 1. *Patient Profile*[a]

Subject no.	Sex	Age	Height	Weight	Age at menopause	Exogenous estrogen	Exogenous progestogen
		yrs	in	lbs	yrs		
1	F	46	63	139	41	Conjugated estrogen 1.25 mg/day	None
2	F	41	63	128	37	E_2 valerate injections and diethylstilbestrol 0.25 mg/day	None
3	F	54	62.5	152	53	Conjugated estrogen 1.25 mg/day	Medroxyprogesterone acetate 10 mg daily 10 days/month
4	F	61	65	203	33	None	None
5	F	36	64	228	28	None	None
6	F	47	69	136	46	None	None
7	F	38	60	112	26	None	None
8	F	41	65.5	146	37	Conjugated estrogen 1.25 mg/day	None
9	F	37	63	184	29	Conjugated estrogen 1.25 mg/day	None
10	M	47	69	215	—	None	None

[a]M, male; F, female.

MATERIALS AND METHODS

Nine healthy postmenopausal women and one male subject volunteered for the study (Table 1). Five women were receiving exogenous estrogens. One woman had previously received progestational agents, but none of the volunteers had taken any progestin within 3 weeks before the onset of the study. The participants were fasting at the onset of the study but were allowed to eat 4 hours after the administration of P. The patients were ambulatory but were without strenuous exercise for the first 6 hours of the study. During the subsequent 18 hours, normal activity and diet were permitted.

P, USP micronized, lot #076UJ, was obtained from The Upjohn Company, Kalamazoo, MI. The particle geometric mean diameter was 11 ± 1.7 μ (particle size: 90% ≤ 20 μ, 95% ≤ 10 μ, and 71% ≤ 5 μ). Micronized P, 100 mg, was placed into #3 plain gelatin capsules (Delk Pharmacy, Columbia, TN).

With subjects fasting, a 21-gauge heparin lock needle (Abbott Intermittent Infusion Set, #4721, Abbott Laboratories, North Chicago, IL) was inserted intravenously at 9:00 A.M. All subjects received 200 mg of micronized P by mouth at 9:05 A.M. Blood was drawn before P administration and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 24.0 hours thereafter. Serum was separated by centrifugation, labeled, and frozen for determinations of P, estradiol (E_2), cortisol, dehydroepiandrosterone sulfate (DHEA-S), follicle-stimulating hormone (FSH), luteinizing hormone (LH), high-density lipoproteins (HDL), triglycerides, cholesterol, serum glutamic pyruvic transaminase (SGPT), bilirubin, and alkaline phosphatase. The blood pressure, pulse, and temperature were monitored at each blood drawing.

Serum alkaline phosphatase, SGPT, bilirubin, HDL, cholesterol, and triglycerides were determined with commercial kits from Mallinckrodt, Inc., St. Louis, MO with the use of the Mallinckrodt Serometer Model 375.

The assays for P, cortisol, FSH, and LH were performed by radioimmunoassay (RIA) with the use of commercial kits obtained from Diagnostic Products Corporation, Los Angeles, CA. Intraassay variations for these hormones were 7.5%, 4.1%, 3.1%, and 3.2%, respectively. The interassay variations were 4.3%, 8.8%, 4.6%, and 5.4%, respectively. The RIAs for E_2 and DHEA-S were performed with kits obtained from Pantex, Santa Monica, CA. Intraassay variations were 5.6% and 6.2%, respectively. Interassay variations were 13.8% and 7.6%, respectively.

Normal midluteal P concentrations for the Diagnostic Products' RIAs were determined in seven healthy women with regular ovulatory cycles. Because luteal phase P concentrations may be pulsatile and vary according to the day of the cycle,[8] serum from each subject was obtained in the morning on 3 separate days in the midluteal phase. These samples were pooled for each individual patient.

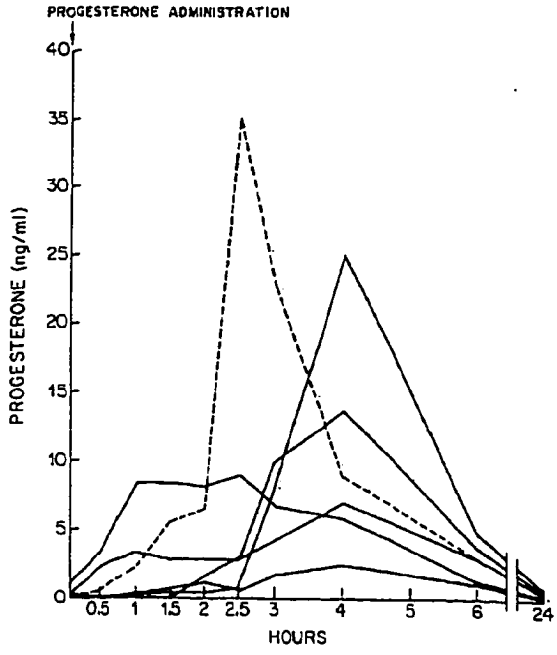

Figure 1
Serial P concentrations after the oral administration of micronized P, 200 mg at time 0; male (– – –) and female (——) subjects with E_2 concentrations < 50 pg/ml.

Data were analyzed by Student's *t*-test and correlation analysis.

RESULTS

Baseline P concentrations were < 1 ng/ml. In all patients, P levels increased to 2 ng/ml after P administration, reaching a peak of 17.0 ± 4.9 ng/ml (mean ± standard error of the mean [SEM]) at an average of 2.8 ± 0.35 hours (Figs. 1 and 2 and Table 2). Peak concentrations of P in this group were not significantly different from mean midluteal levels in the control cycles (14.1 ± 2.7 ng/ml).

The rate of absorption was variable (Figs. 1 and 2). P concentrations rose above 1 ng/ml in three patients by 0.5 hours; six patients at 1.0 hours, seven patients at 1.5 hours, and nine patients at 2.0 hours.

All subjects exhibited a significant elevation of P over baseline levels that persisted for at least 6 hours after a single oral dose and that subsequently returned to initial levels by 24 hours (Fig. 3).

Peak P concentrations were positively correlated with serum E_2 concentrations measured concomitantly ($r = 0.636$, $P < 0.02$). However, there was no significant change in mean E_2 levels at any of the sampling intervals (Table 2).

No significant change in blood pressure, temperature, pulse rate, FSH, LH, bilirubin, alkaline phosphatase, SGPT, or lipids was observed between the time of baseline determination, peak P concentration, and 24 hours after administration (Table 2).

No major complications were reported in these subjects during the 24-hour study interval. Minor side effects included drowsiness in three women. This symptom was noted between 1 and 3 hours after oral administration of P, within 1 hour of the measurement of peak P concentration in each individual. One subject complained of exacerbated hot flashes at 24 hours. No gastrointestinal side effects during the 24-hour study interval were reported.

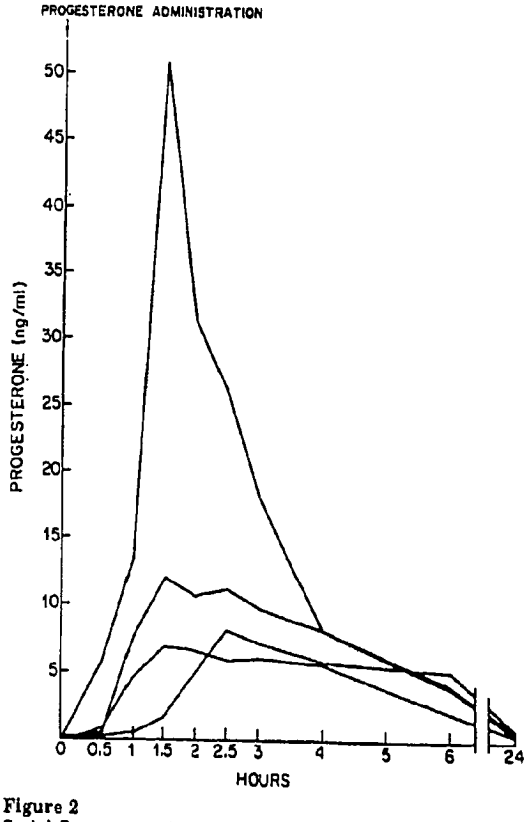

Figure 2
Serial P concentrations after the oral administration of micronized P, 200 mg at time 0. Female subjects with E_2 concentrations > 50 pg/ml.

Table 2. *Serum Concentrations of Steroids, Enzymes, and Lipids in Female Subjects (n = 9) Receiving Oral Micronized P 200 mg at Time 0*

Test	Units[a]	Time				
		0	2	4	6	24
				hrs		
P	ng/ml	0.2 ± 0.1[b]	7.5 ± 3.1[c]	9.1 ± 2.2[d]	3.2 ± 4.1[d]	0.6 ± 0.1
E_2	pg/ml	72 ± 24	57 ± 16	60 ± 18	62 ± 19	56 ± 14
DHEA-S	ng/ml	1603 ± 614	1488 ± 578	1646 ± 611	1713 ± 590	1860 ± 688
FSH	mIU/ml	70 ± 11	63 ± 13	65 ± 11	73 ± 12	73 ± 12
LH	mIU/ml	68 ± 13	69 ± 12	69 ± 12	73 ± 10	74 ± 13
Cortisol	µg/dl	12 ± 3				11 ± 2
Aldosterone	ng/dl	18 ± 4				18 ± 2
Cholesterol[e]	mg/dl	284 ± 19				279 ± 20
HDL[e]	mg/dl	43 ± 4				43 ± 4
Triglycerides[e]	mg/dl	190 ± 23				188 ± 19
Alkaline phosphatase[e]	Bodansky U/dl	4.3 ± 0.8				4.3 ± 0.5
SGPT[e]	IU/l	11 ± 0.2				11 ± 1
Bilirubin[e]	mg/dl	0.2 ± 0.1				0.2 ± 0.1

[a]All values are recorded as mean ± SEM.
[b]Statistical comparison of baseline values to subsequent measurements by Student's *t*-test. All comparisons not significant ($P > 0.05$), except as noted.
[c]$P < 0.05$.
[d]$P < 0.001$.
[e]Values include one male subject ($n = 10$).

DISCUSSION

Natural P has not been used clinically as an oral preparation because of reportedly poor gastrointestinal absorption and a short biologic half-life.[5, 7] However, in 1978, Kincl et al.[5] demonstrated that nonmicronized P on a lactose carrier in gelatin capsules rapidly increased serum P concentrations in male volunteers. An oral dose of 100 mg of nonmicronized P produced mean serum concentrations that peaked at 2 hours, with a mean of 8.6 ng/ml (range, 3.8 to 13.4 ng/ml), and declined rapidly to 3.2 ng/ml by 4 hours.[5] Whitehead et al.[1] subsequently noted that nonmicronized P administered orally to five postmenopausal women for 5 consecutive days resulted in peak P concentrations of 9.5 ng/ml. In these subjects, a sustained elevation of P was maintained for more than 96 hours after the 5-day loading dose.

Investigation of methods to increase the bioavailability of oral steroids resulted in experiments that indicate that a reduction in the particle size of P by micronization permits increased aqueous dissolution in the intestine and an increased plasma concentration of P in male rats.[5] Subsequently, in preliminary human experiments, Morville et al.[2] reported mean peak P concentrations of 12.6 ng/ml after oral administration of micronized P dissolved in oil.

The present study evaluates the bioavailability and short-term toxicity of a simple oral preparation of micronized P. Gelatin capsules were chosen for simplicity and because minimal drug migration into the capsule shell was anticipated.[9]

After an overnight fast, a single oral dose of micronized P, 200 mg, prompted a significant increase in serum P concentrations in all patients

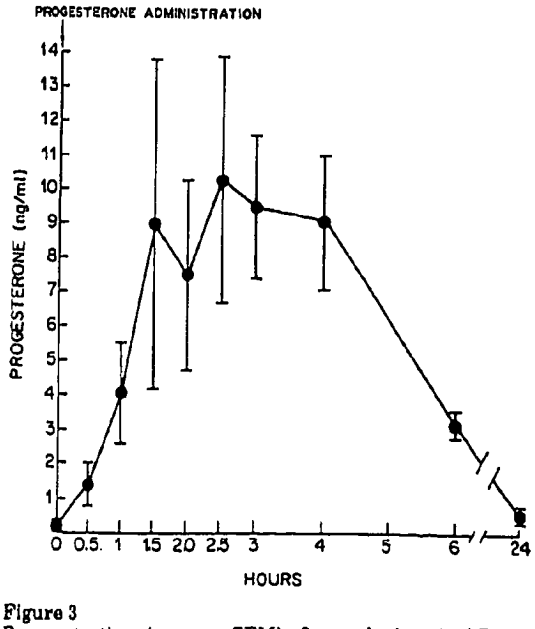

Figure 3
P concentrations (mean ± SEM) after oral micronized P, 200 mg at time 0.

by 2 hours. Mean peak concentrations (17.0 ± 4.9 ng/ml) appeared to be more than double those reported after 100 mg of nonmicronized P[1, 5] and higher than 200 mg of micronized P in oil.[2] An accurate comparison of peak P concentrations after the various oral preparations is not possible because of the difference in RIA techniques employed.

P concentrations began to decline 4 hours after administration but remained significantly elevated for more than 6 hours, returning to baseline levels by 24 hours after administration. The time course of P absorption and metabolism is similar to that reported by Nillius and Johansson[10] to occur after vaginal or rectal administration of nonmicronized P, 100 mg, in suppository form.

Wide interpatient variability in serum P concentrations was observed. This may be due to individual differences in the site and rate of absorption, clearance rates, and extent of absorption of P into fatty tissues. Such a variability in absorption could have significant impact on the clinical efficacy of oral P therapy.

Previous studies have demonstrated that P taken orally is physiologically active which produces a significant increase in tissue P concentrations in myometrium, endometrium, and breast[2, 4] and induces histologic and biochemical changes in the endometrium after 10 days of administration in estrogen-primed postmenopausal women.[6]

Cortisol, aldosterone, and E_2 concentrations in these subjects did not change significantly over the course of the study, which confirms minimal conversion of P to these steroids, as reported previously. However, a significant positive correlation was found between baseline E_2 concentrations and the peak P levels achieved. Villanueva et al.[11] have demonstrated that the most rapid absorption and highest levels of P after vaginal application occurred in those postmenopausal women who were receiving estrogen. The authors hypothesized that anatomic and metabolic differences in the estrogen-treated group were responsible for improved P absorption.[11] It is unknown whether estrogen has a similar effect on the intestinal absorption and hepatic metabolism of P after oral administration.

No metabolic effects were seen in the parameters measured during the 24-hour period of observation in this study, and no major side effects were reported.

Our data clearly demonstrate that a single oral dose of 200 mg of micronized P provides P concentrations within or above the levels normally seen during the luteal phase. Further long-term studies are required to evaluate the clinical efficacy, side effects, and optimal dosage interval of prolonged oral administration of micronized P.

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